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Remarks

A. Status of the Claims

Claims 1-19, 23, 25, 30, 32 and 34-38 are canceled without prejudice.

Claims 20-22, 24, 26-29, 31 and 33 remain pending in the application and have been amended herewith without prejudice in accordance with the foregoing claim listing.

In particular, independent Claims 20 and 27 have been amended to remove the negative claim limitation "not hydroxylated at the 1-alpha position." Applicant has further amended independent claims 20 and 27 to clarify that the claimed compounds are "capable of being hydroxylated by vitamin D 1-alpha hydroxylase." Support for the amended language can be found throughout the specification, e.g., at page 9, lines 13-21, page 12, lines 2-6, page 18, line 25 through page 19, line 30 as well as Fig. 1.

In addition, Claim 20 has been amended to add the recitation of pancreatic cell cancer. This recitation was inadvertently omitted in transcribing the claim in a previous amendment. The recitation of pancreatic cell cancer was, and has been, present in claim 27. Accordingly, the current amendment adding "pancreatic cell cancer" to claim 20 merely makes the scope of the two independent claims, claims 20 and 27, consistent with one another.

Applicant respectfully submits that no new matter is added by virtue of these amendments.

B. Telephonic interview summary

Applicant and applicant's attorney further wish to thank the Examiner for granting the telephonic interview on August 11, 2008. In that interview, applicant's attorney clarified for the Examiner the proposed amendment to the claims which are being made herein, in order to remove the objected-to negative limitation.

Also discussed was the combination of the Getzenberg and Haussler references cited in the current office Action. Applicant clarified that Haussler was limited to bone and

mineral metabolism, rather than inhibition of tumor or cancer cells. Applicant further pointed out that the presence of vitamin D receptors in a target cell did not lead to the conclusion that 25-hydroxyvitamin D could be readily substituted for 1,25-dihydroxyvitamin D because the result was unpredictable. At the time of the invention, growth of vascular cells (which have the vitamin D receptor) is stimulated by vitamin D – the opposite effect claimed by the subject method.

Other issues discussed in the telephonic interview included the fact that the enzyme, vitamin D-1α hydroxylase, was not previously known to be present in the target cells as claimed and that the presence of this enzyme in the target tissues allows much lower, and non-toxic, doses of the claimed prodrugs to be used. This is in contrast to the teaching of Haussler, which does not provide any information regarding the presence of the enzyme in the claimed target cells, and relies on much higher doses (considered to be dangerous and potentially toxic levels) of the prodrugs for their conversion by the kidney into 1,25-dihydrxyvitamin D.

It was suggested by the Examiner to present the information discussed in the telephonic interview as part of an expert declaration by the inventor. Applicant appreciates the helpful suggestion and presents, as part of this Reply, a Declaration under Rule 132 by the inventor, Dr. Gary Schwartz, to provide the information on the record.

C. **Withdrawal of previous rejections**

Applicant appreciates the Examiner's careful consideration of the previous amendments and accompanying remarks, and the consequent withdrawal of the prior rejections. Specifically, the rejection of claims 20-38 under 35 USC §112, second paragraph, the rejection of claims 34-38 under 35 USC §112, first paragraph, and the refection of claims 20, 22-23, 25-27, 29-30, and 32-33 under 35 USC §102(b) in view of Raina, et al., are withdrawn in view of applicant's amendments.

Certain new rejections have been asserted in the instant Office Action. These new rejections are addressed below:

D. **Rejections – 35 U.S.C. §112**

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 USC §112, first paragraph, for failing to comply with the written description requirement. Specifically, this new matter rejection is based on the negative limitation included as part of the previous amendments reciting that the method includes the use of compounds "not hydroxylated at the 1-alpha position. Although applicants respectfully traverse, and maintain that such limitation is clear from the specification as filed, this rejection is rendered moot by the deletion of the negative limitation in the current amendments.

The current amendments now provide the same concept as the positive recitation that the "25-hydroxyvitamin D, or an analog, salt, or derivative thereof [is] capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ. Thus, the claimed method involves only those compounds "not hydroxylated at the 1-alpha position," since those compounds are already hydroxylated at the 1-position, and are not "capable of being hydroxylated by vitamin D 1-alpha hydroxylase in a target organ." Support for the amended language can be found throughout the specification, e.g., at page 9, lines 13-21, page 12, lines 2-6, page 18, line 25 through page 19, line 30 as well as Fig. 1.

In view of the amendment to the claims, which is clearly supported in the specification, applicant believes the claims, as amended, meet the written description requirement. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

E. **Rejections – 35 U.S.C. § 103**

Claims 20-22, 24, 26-29, 31 and 33 also stand rejected under 35 U.S.C. § 103 as being unpatentable over Getzenberg et al. (Getzenberg) in view of Haussler et al. (Haussler).

In particular, the instant Office Action, at page 4, states that Getzenberg teaches a method of inhibiting prostate tumor and/or cancer growth in an animal which comprises administering calcitriol (1,25-D3) and other less hypercalcemic analogues. However, it is acknowledged in the Office Action that Getzenberg is defective in its teaching in that it *does not* teach the administration of the claimed compound, 25-hydroxyvitamin D.

Haussler is then asserted in the Office Action as teaching that analogs of calcitriol such as 25-hydroxyvitamin D (calcifediol) are safe and effective alternative therapeutic agents to Vitamin D, and that calcifediol is has been shown to substitute for calcitriol at receptor sites. The Office Action thus concludes that Haussler in combination with Getzenberg renders obvious the claimed invention.

Applicant respectfully traverses this rejection and disagrees with the conclusion drawn in the Office Action. Haussler does not cure the defects of Getzenberg because Haussler is limited to the to treatment of bone and mineral metabolism disorders (see, for example, the Abstract as well as column 1, lines 1-27, column 2, lines 4-13, of Haussler). While Haussler may describe calcitriol as the most active natural metabolite of Vitamin D, and further that analogs such as calcifediol (25-hydroxyvitamin D) are safe and effective alternative therapeutic agents to Vitamin D, this teaching is strictly limited to the ability of calcifediol to treat disorders of bone and mineral metabolism – not inhibition of tumor or cancer cells as claimed for the subject invention.

Nowhere does Haussler even remotely suggest a therapeutic indication for any of the claimed compounds as a treatment for cancer, much less the inhibition of tumor cell proliferation in the specific tissues set forth in the claimed invention. Moreover, there is absolutely no appreciation or even a remote mention in Haussler of 1-alpha hydroxylase in the claimed target tissues or how its presence could be utilized in a novel manner to convert 25-OH vitamin D to 1,25-dihydroxyvitamin D to inhibit tumor cells or treat cancer. Thus, Haussler provides no suggestion to motivate or otherwise lead a person of ordinary skill in the art to administer 25-OH vitamin D for treatment of tumors as claimed.

The Examiner's attention is respectfully directed to the current claims, as amended, which are drawn to a method for inhibiting specific types of tumor cells (i.e. prostate, breast, skin, colon, pancreatic and lung) by administering 25-hydroxyvitamin D or an analog, salt or derivative thereof. Importantly, the unexpected result provided by the claimed method is related to the presence of the vitamin D-1α hydroxylase enzyme in the target cells. Before applicant's discovery, the hydroxylase enzyme was thought to be present only in kidney tissue (e.g., see Haussler p.841, column 3). Therefore, the capability of 25-hydroxyvitamin D to become hydroxylated at the 1-alpha position *at the target tissue site*, was previously unknown in prostate cells and certain other cells, as claimed.

Applicant further notes the comment in the Office Action that, according to Haussler, calcifediol has been shown to substitute for calcitriol at receptor sites. However, as provided in the expert declaration of Dr. Gary Schwartz, submitted herewith as part of the instant Reply, the mere affinity of a receptor for more than one ligand does not by itself constitute the premise that one ligand can be effectively substituted for another ligand to achieve the same therapeutic effects. Moreover, applicant would point out that the effect of vitamin D or any of its congeners on cells cannot be predicted merely from knowledge that these cells possess vitamin D receptors (i.e., receptors for $1,25(OH)_2$ vitamin D, or VDR). For example, vascular cells (like prostate cells) possess vitamin D receptors. However $1,25(OH)_2$ vitamin D is a potent growth stimulator, not a growth inhibitor, of vascular cells. The 1,25-dihydroxyvitamin D_3 binds specifically to rat vascular smooth muscle cells and stimulates their proliferation in vitro. Additionally, at the time of the present invention, there was no known mechanism for the prostate to respond to 25-OH vitamin D.

Additionally, as further addressed in the expert declaration submitted by Dr. Schwartz, in order for 25-OH vitamin D to substitute for $1,25(OH)_2$ vitamin D, Haussler teaches (in the context of bone and mineral metabolism disorders) that "therapeutically effective blood levels of 25(OH) vitamin D" must be at least 500 times higher than that of $1,25(OH)_2D$ (since 25-OH vitamin D has $1/500^{th}$ the affinity of $1,25(OH)_2$ vitamin D for the vitamin D receptor). The method of the present invention does not require these excessively high systemic levels since the target cells, e.g., prostate cells convert 25-OH vitamin D into $1,25(OH)_2$ vitamin D *intra-prostatically* to inhibit proliferation of prostate tumor cells. Importantly, the present invention harnesses the active conversion of 25-OH vitamin D to $1,25(OH)_2$ vitamin D, rather than overwhelming the Vitamin D receptor with pharmacologic (and possibly toxic) levels of 25-OH vitamin D.

Moreover, the doses described by Haussler raise *serum* levels of 25-hydroxyvitamin D well above the concentration of 350 nmol/L which, as stated in the subject application, is considered "dangerous" to the health of the individual. This dangerous serum concentration is exactly what is avoided by the subject method, where serum concentrations are limited to non-toxic concentrations, namely, between 25 and 250 nmol/L as expressly claimed.

Haussler does not therefore provide a teaching that would lead a person of ordinary skill in the art to substitute 25-hydroxyvitamin D for the 1,25-dihydroxyvitamin D taught by Getzenberg, to prevent or treat certain cancers, such as prostate cancer, especially using the claimed low levels of effective in providing intracellular levels of 1,25-dihydroxyvitamin D within the normal range of less than 250 nmol/L. As such, applicant maintain that the references of Getzenberg and Haussler, either taken alone or together, do not render obvious the subject method set forth in the claims as amended herewith. Accordingly it is respectfully requested that the rejection under 35 USC 103(a) be reconsidered and withdrawn.

In accordance with the foregoing amendments to the claims and accompanying remarks, applicant believes this case to be in condition for allowance, the action of which is earnestly solicited.

Applicants further invite the Examiner to call the undersigned if clarification is needed on any aspect of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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/Ted W. Whitlock/

Ted W. Whitlock
Registration No. 36,965
5323 SW 38th Avenue
Ft. Lauderdale, Florida 33312
Ph: 954-986-2119
Fax: 954-986-2120